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REMARKS

Claims 1, 10, 17, 23 and 24 are amended. No claims are added or canceled. Claims 1 - 25 are in the case.

The specification is amended by the correction of three typographical errors. In the first case, the spelling of the word "perforin" has been corrected. Correct spelling of the word is shown later on the same page and line and again at least at page 25, line 22. The recitation of "Figure 2" at page 10, line 25, was corrected to refer to Figure 5, so that the number actually agrees with the description of the figure given at that point. The description refers to an illustration of the internalization and degradation mechanism proposed for RID, and this mechanism is obviously shown in Figure 5, rather than in Figure 2. On page 12, line 21, the term "RIDα-β" was corrected to read "RIDα-S". No "RIDα-β" is known to be involved in the present invention.

The specification has also been amended by the addition of a Sequence Listing according to 37 CFR §1.821(c), and by the addition in the text of sequence identification numbers, as provided by 37 CFR §1.821(d), that correspond with the Sequence Listing.

Claims 1, 10, 17, 23 and 24 have been amended to clarify the structure of the RID complex as being one that includes a RIDα polypeptide and a RIDβ polypeptide. Support for this is found throughout the specification, but at least at page 4, lines 25 and 26.

Claim 23 has been amended to clarify what is claimed by replacing the terms "and a carrier suitable for facilitating delivery of the RID complex into a cell" with "in a pharmaceutically acceptable excipient". The latter terms are defined in the specification at least at page 15, line 35 to page 16, line 18.

A Sequence Listing that is in accord with 37 CFR §1.821(c) has been provided and is attached to this amendment. A copy of the Sequence Listing in computer readable form in accord with 37 CFR §1.821(e) is also enclosed on a diskette. To conform with 37 CFR §1.821(f), it is hereby stated that the information recorded in computer readable form is identical to the written sequence listing.

No new matter has been added.

Rejection of claims 1 - 3, 5 - 12, 14 - 19 and 21 - 24 under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

It is respectfully requested that the rejection of claims 1 - 3, 5 - 12, 14 - 19 and 21 - 24 under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention, be reconsidered in view of the amendments to the claims and the reasons that are discussed below and be withdrawn.

The rejected independent claims are as follows: Claim 1 describes a method for inhibiting apoptosis of a cell by treating the cell with an effective amount of a RID complex having a RIDα and a RIDβ polypeptide. Claim 10 describes the inhibition of apoptosis of target cells in a patient by treating the patient with an effective amount of a RID complex. Claim 17 describes a method for decreasing leukocyte apoptosis in a patient by withdrawing leukocytes from the patient, treating them with RID, and administering the treated leukocytes back to the patient. Claim 23 describes a composition comprising RID and an excipient, and claim 24 describes a recombinant adenovirus containing a polynucleotide encoding RID operably linked to a promoter, where the adenovirus is replication defective and the polynucleotide is expressed upon infection of a eukaryotic cell with the adenovirus.

The Action argues that the claims are not enabled for treatment of cells *in vitro* because the specification fails to supply critical guidance as to the effective amounts, effective frequencies and stability of delivery of the complex or gene, or vectors containing the RID complex sequence and promoters regulating the expression of the RID sequence to obtain a meaningful supply of expressed RID sequence into the target cell. In particular, the Action states that a protocol is not described for vectors comprising the RID sequence that integrate into the genome and supply sufficient RID complex function to provide inhibition of cell death. However, claims that describe the recombinant adenovirus vector containing a polynucleotide encoding a RID complex as comprising the 231-10 vector have not been rejected.

The Action goes on to argue that the specification does not provide any readily available assays under the meaning of *In re Wands*, that permit the determination of the complexes of RID, such as, prolong expression, cellular stability, cellular response to RID complex and cellular response to adenovirus vector. Moreover, the Action maintains that no guidance as to the RID complex function is supplied by any of the various examples that

incorporate the RID complex usage, and concludes that a skilled artisan would be unable to implement the claimed invention without undue experimentation.

The Action cites *Genentech v. Novo Nordisk A/S*, 42 USPQ 2d 1001 (Fed. Cir. 1997) as stating that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable", and that "tossing out the mere germ of an idea does not constitute an enabling disclosure". Yet, there is no indication regarding how such citation is applicable to the present application.

In *Genentech*, the patentee's claim described a method for producing a protein by expressing DNA coding for human growth hormone and cleaving the conjugate protein that was produced to produce an active hGH fragment. The court found the specification to not be enabling for such a claim when it did not "suggest a single amino acid sequence out of the virtually infinite range of possibilities, that would yield hGH in a useful form when cleaved from the conjugate protein", and suggested no enzyme that would cleave the conjugated protein into an active fragment. The court found that when the specification did not disclose "any specific starting material or ... any of the conditions under which a process can be carried out", undue experimentation would be required to carry out the claimed method.

It is maintained that the present case is significantly different from the case addressed in *Genentech*, and fully meets the standard for enablement laid out in that case.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *Genentech* at 1004. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public [having ordinary skill in the pertinent art] to understand and carry out the invention. *Genentech* at 1005. Indeed, a specification need not describe -- and best omits -- that which is well known in the art. *In re Buchner*, 18 USPQ 2d 1331, 1332 (Fed. Cir. 1991). But, the specification, not knowledge in the art, must supply the novel aspects of an invention. See, *Genentech* at 1005.

It is maintained that the present specification -- in stark contrast to the inadequate specification in *Genentech* -- fully enables the present claims to the extent required by 35 USC §112, first paragraph by providing the requisite enabling disclosure for each and every one of the novel aspects of the claimed invention. A detailed discussion of each of these factors is presented by the inventor, Dr. Wold, in his Declaration under 37 CFR §1.132, which is attached to and incorporated into this Response. Dr. Wold has also enclosed copies of several references that are

not prior art for this application, but which are useful to explain or define basic points of the technology being discussed.

Dr. Wold's Declaration addresses seriatim each of the objections and arguments that were raised in the Action. In the Declaration, Dr. Wold points out where certain guidance and enabling disclosure is provided in the specification and explains its context with the known art.

In the Action, it is argued that guidance is not provided for the effective amounts, frequencies and stability of the RID complex, and vectors comprising genes encoding the RID complex. However, it is maintained that such guidance is provided, in significant detail, at least in Example 2, where plasmids expressing RID component polypeptides are used to transfect mammalian cells, and the effect of the presence and absence of the RID complex upon apoptosis of the cells is demonstrated; in Example 3, where an adenovirus vector was used to transfect human cells to demonstrate clearing of Fas; in Example 4, where human A549 cells were infected with viral vectors that were positive or negative for the expression of RID complex polypeptides, and clearing of Fas from the cell surface was measured; in Example 5, where human MCF7 cells were infected with wild-type or mutant Adenovirus to demonstrate that signal receptors are degraded in lysosomes; in Example 6, where COS cells were transiently transfected with plasmids containing various RID complex components and it was shown that Fas was cleared from the surface of the cells by the complete RID complex; in Example 7, where lymphocytes withdrawn from mice infected with influenza virus were activated and incubated with RID+ and RID- mouse cells to show that RID inhibited CTL cell killing through the Fas pathway; and in Example 8, where human HeLa cells infected with viral RID polynucleotides and with 231-10 plasmid RID polynucleotides showed the internalization and destruction of Fas and TNFR1.

Thus, the inventor has described in detail how the RID complex can be administered to several different types of cells, including several different types of human cells, and by several different vectors. Successful treatment of the cells is shown in each of the examples presented.

The Action particularly notes the lack of a protocol for vectors comprising RID complex that integrate into the genome and supply sufficient RID to inhibit apoptosis. As Dr. Wold has noted on page 5 of his Declaration, integration of the RID sequences into genomic DNA is not required for the successful practice of the invention. However, it is maintained that in view of the teachings of the specification regarding the structure of the 231-10 plasmid, one of

ordinary skill could easily provide for integration of a RID sequence into genomic DNA if such were his/her desire.

In response to argument in the Action that the assays necessary for practicing the invention were not disclosed, the Declaration also provides a detailed account of where enablement is provided in the specification for assays for the determination of RID expression and the effect of RID presence on apoptosis.

The assertion in the Action that "there is not guidance as to the RID complex function to be supplied by any of the various examples that incorporate the RID complex usage" is not fully understood. However, if it is meant that the examples in which RID is used to treat cells provide no guidance as to the function of RID, then such assertion is respectfully rejected. In particular, Examples 4, 5, 7 and 8 report experiments designed particularly to elucidate the function of RID activity in the cell. Each of these examples include data that is interpreted to define the function of the RID complex. It is maintained that this information would be of great value to a skilled practitioner in understanding and being able to practice the full scope of the present invention without undue experimentation.

The Action reviewed the prior art for citations suggesting unpredictability in the art of gene therapy, and, in particular, gene therapy applied to the treatment of human disease. However, as Dr. Wold has discussed on page 6 of his Declaration, the cited art is not applicable to the present invention, because the claimed invention is not "gene therapy" in the sense described in the cited art. The present invention simply introduces two "foreign" genes into a cell in order to express the encoded polypeptides, rather than to attempt to correct a genetic defect -- as in classic "gene therapy". Also on pages 6 - 8 of his Declaration, Dr. Wold points out why the cited references by Deigner *et al.* and Tio *et al.* would not support the arguments that are made in the Action regarding the unpredictability of the modulation of apoptosis and the limitation of adenovirus-mediated gene therapy.

On page 6 of the Action, it is argued that the specification fails to provide guidance for *ex vivo* treatment of cells. In particular, it is argued that no working examples are provided that illustrate the withdrawal of leukocytes, the *ex vivo* treatment of the leukocytes, and the administration of the treated leukocytes back to the patient. However, it is believed that the lack of working examples to illustrate every detail of the invention is not determinative in an enablement inquiry. Nothing more than objective enablement is required, and therefore it is irrelevant whether a teaching is provided through broad terminology or illustrative examples. *In re Robins*, 166 USPQ 552, 555 (C.C.P.A. 1970). At page 8 of his Declaration, Dr. Wold has

described why a skilled artisan would have been able to understand and practice *ex vivo* treatment of cells after reading the specification and in view of the known art.

In response to the statement of page 6 of the Action, that controls were not run for Example 9, Dr. Wold, on page 8 of his Declaration, describes the controls that were run in that example, and points out where the description of these controls can be found in the specification.

It is maintained that the present specification, including the drawings, the Sequence Listing and the claims, when read in view of the art known at the time of the invention, would have fully enabled a skilled practitioner to understand and practice each claim to its full scope. Accordingly, it is respectfully requested that this rejection be reconsidered and withdrawn.

Rejection of claims 4, 13, 20 and 25 under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

It is respectfully requested that the rejection of claims 4, 13, 20 and 25 under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention, be reconsidered in view of the amendments to the claims and the reasons that are discussed below and be withdrawn.

The rejected claims describe the adenovirus vector as the 231-10 plasmid. The rejection states that the 231-10 plasmid must be obtainable by a repeatable method set forth in the specification, or otherwise to be readily available to the public. The Action argues that the specification does not set forth a repeatable process to obtain the 231-10 plasmid, and it is not apparent that the plasmid has been deposited.

It is maintained that the specification does, in fact, provide a repeatable method for the production of the 231-10 plasmid. Support for this statement is discussed by Dr. Wold on page 9 of his Declaration. In brief, Example 10 of the specification describes in detail how to construct the plasmid. Figure 27 shows the schematic illustration of the plasmid and Figure 28 (and SEQ ID NO:5) provide the complete double-stranded nucleotide sequence for the entire plasmid. It is believed that, armed with such information, a skilled practitioner would easily and repeatably be able to construct the 231-10 plasmid.

Accordingly, it is respectfully requested that the rejection of these claims be reconsidered and withdrawn.

Rejection of claims 1 - 25 under 35 USC §112, second paragraph, as being vague and indefinite.

It is respectfully requested that the rejection of claims 1 - 25 under 35 USC §112, second paragraph, as being vague and indefinite, be reconsidered in view of the amendments to the claims and the reasons that are discussed below and be withdrawn.

In claims 1 - 25, the use of the term "RID" was objected to as being vague and indefinite. Although it is believed that the term "RID" is clearly defined in the specification, at least at page 4, lines 25, 26; page 5, lines 18 - 21; and page 11, lines 31, 32, all independent claims have been amended to clarify that the RID complex that is the subject of the claims comprises a RIDα polypeptide and a RIDβ polypeptide. It is believed that a skilled practitioner would readily be able to identify the structure being described.

In claim 23, the use of the term "suitable" was objected to. The term has been removed and the claim has been amended to describe the composition as including a "pharmaceutically acceptable excipient". These terms are defined in the specification and their meaning is well known to a skilled artisan.

Accordingly, it is respectfully requested that this rejection be reconsidered and withdrawn.

Statement that the claims are free of prior art:

The recognition in the Action that the claims are free of the prior art is noted with appreciation.

Request for reconsideration:

It is respectfully requested that the amendments that are described above be entered into the case and that the amended claims be reconsidered in view of the amendments and the remarks that follow the amendments. It is believed that the claims are now in condition for allowance and such action is respectfully requested. If some or all of the claims are deemed to

not be allowable, it is requested that the Examiner contact the undersigned attorney at the telephone number give below in order that any remaining issues can be resolved.

Respectfully submitted,

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